Remarks/Arguments:

Claims 11, 14-16, 22-25, 31-34, 40-43, 50-51, 54-57, 64-70, and 75-80 are canceled without prejudice. Claims 1, 6, 12-13, 17, 26, 35, 44, 52-53, and 58 are amended. New claims 81-96 are added. Support for these amendments can be found throughout the application as originally filed. No new matter is introduced.

Claims 1-10, 12-13, 17-21, 26-30, 35-39, 44-49, 52-53, 58-63, 71-74, and 81-96 are pending. Claims 4, 9, 20, 29, 38, 48, 62, and 71-73 are withdrawn from consideration as being directed to non-elected inventions. Reexamination and reconsideration of the application, as amended, are respectfully requested.

PRIORITY

The Examiner stated that the provisional application from which the present application claims priority does not disclose (1) plasma samples, (2) colon, breast, or brain cancer, (3) progression of cancer, or (4) RLM or ITM melanoma. Applicants respectfully disagree. More specifically, the provisional application states, e.g., at page 6, lines 25-29: "The inventors identified circulating tumor microsatellites with LOH in the acellular plasma of patients with melanoma (10-12). The plasma LOH correlated with genetic alterations present in the respective melanoma tumors and poor disease outcome (10)." (Emphasis added.) Further, the provisional application states, e.g., at page 2, lines 4-5: "In particular, this invention relates to the detection of the loss of the APAF-1 gene and the relationship this gene loss has to tumor progression." (Emphasis added.) Since one skilled in the art would know that "tumor" is a general term encompassing all types of tumor including colon, breast, and brain cancer, these cancers are within the scope of the invention. In addition, the provisional application states, e.g., at page 4, lines 17-18: "Figure 3c shows correlation of *APAF-1* LOH in AJCC Stage III melanoma (regional lymph node and in-transit metastasis) tumor with survival." (Emphasis added.) Since the provisional application, in view of the knowledge in the art, sufficiently teaches (1) plasma samples, (2) colon, breast, or brain cancer, (3) progression of cancer, and (4)

RLM or ITM melanoma, the present application is fully entitled to its claimed priority. Withdrawal of the Examiner's statements is thus respectfully requested.

CLAIM OBJECTIONS

The Examiner objected to claim 1 for reciting "comprisingproviding." Applicants have added a colon after "comprising" to separate it from "providing." The Examiner also objected to claim 65 for a spelling error. Claim 65 has been canceled without prejudice, rendering this objection moot. Applicants respectfully request that the objections be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH - ENABLEMENT

Claims 1-3, 5-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 stand rejected for lack of enablement. More specifically, the Examiner stated that the specification does not provide sufficient support for "any" marker at 12q22-23, "any" cancer, or "any" subject.

Without acquiescence to the Examiner's statement and for the sole purpose of moving this application forward, Applicants have amended the claims such that the DNA markers at 12q22-23 are limited to those present in the region extending from D12S1657 to D12S346 (e.g., claim 1) or those including D12S1657, D12S393, D12S1706, and D12S346 (e.g., claims 6, 17, 26, 35, 44, 58, and 93). Likewise, the cancer is now limited to melanoma, colon cancer, or breast cancer; the subject is limited to human.

In particular, amended claim 1 is directed to a method of detecting DNA markers in the 12q22-23 region. The method involves two steps: (1) providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject, and (2) detecting one or more DNA markers in the 12q22-23 region extending from D12S1657 to D12S346 on the DNA. Amended claim 1 is fully enabled by the specification. For instance, Example 2 at page 31, line 9 – page 40,

line 2 of the specification demonstrates that four markers in the 12q22-23 region were detected in serum samples containing acellular DNA: D12S1657, D12S393, D12S1706, and D12S346, indicating that chromosome 12 present in these samples include at least the region between D12S1657 and D12S346. Therefore, markers within this region are detectable.

Amended claim 6 is directed to a method of detecting melanoma. The method involves two steps: (1) providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 is indicative of melanoma. Amended claim 6 is fully enabled by the specification. For instance, Example 2 at page 31, line 9 – page 40, line 2 of the specification demonstrates that, compared to the control DNA, LOH of the markers was found in serum samples containing acellular DNA from melanoma patients.

New claim 93 is directed to a method of detecting colon or breast cancer. The method involves two steps: (1) providing a sample containing DNA from a human subject; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 is indicative of colon or breast cancer. New claim 93 is fully enabled by the specification. For instance, Example 2 at page 31, line 9 – page 40, line 2 of the specification demonstrates that, compared to the control DNA, LOH of the markers was found in serum samples containing acellular DNA from colon and breast cancer patients. Note that the control DNA was obtained from the patients' peripheral blood lymphocytes, and the LOH on the sample DNA was identified by comparison to the control DNA on which the LOH was 0% (page 32, lines 27-29 and page 33, lines 13-15 of the specification). Therefore, the LOH on the sample DNA was significantly different from the LOH on the control DNA ($p<0.05$), i.e., the LOH of the markers was significantly higher in colon and breast cancer.

Amended claim 17 is directed to a method of staging melanoma or colon cancer. The method involves two steps: (1) providing a sample containing DNA from a human subject suffering from melanoma or colon cancer; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a high probability of a metastatic cancer. Similarly, amended claim 26 is directed to a method of monitoring progression of melanoma or colon cancer. The method involves two steps: (1) providing a sample containing DNA from a human subject suffering from melanoma or colon cancer; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a high probability of a progressing cancer.

Amended claims 17 and 26 are fully enabled by the specification. For instance, Example 1 at page 18, line 11 – page 31, line 7 of the specification demonstrates that LOH of the markers was significantly higher in metastatic melanoma than in primary melanoma ($p=0.02$). The statistical relevance of LOH of the markers in colon cancer has been confirmed in an article published by Umetani et al. at Oncogene (2004) 23(50):8292-8300, a copy of which is attached hereto as Exhibit A. It was found that LOH of the markers was significantly higher in liver metastases than in primary CRCs ($p=0.038$) (Umetani et al., page 8293, left column, lines 17-21 of the last paragraph).

Amended claim 35 is directed to a method of predicting the efficacy of a melanoma biochemotherapy. The method involves two steps: (1) providing a sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of a biochemotherapy; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy. Similarly, amended claim 58 is directed to a method of determining the probability of responsiveness to a melanoma biochemotherapy.

The method involves two steps: (1) providing a sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of a biochemotherapy; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy. Amended claims 35 and 58 are fully enabled by the specification. For instance, Example 2 at page 31, line 9 – page 40, line 2 of the specification demonstrates that LOH of the markers was significantly lower in the responder group than in the non-responder group (p=0.029).

Amended claim 44 is directed to a method of determining the probability of survival. The method involves two steps: (1) providing a sample containing DNA from a human subject suffering from a stage III or IV melanoma; and (2) analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 on the DNA. LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of survival. Amended claim 44 is fully enabled by the specification. For instance, both Example 1 at page 18, line 11 – page 31, line 7 of the specification and Example 2 at page 31, line 9 – page 40, line 2 of the specification demonstrate that LOH of the markers was significantly associated with decreased survival (p=0.049 and p=0.046). In particular, in patients with AJCC stage III/IV melanoma, the presence of APAF-1 LOH in their metastatic tumor was significantly associated with a decreased overall survival at a mean follow-up of 27 months (log-rank test, p=0.049), although the difference in overall survival of patients with APAF-1 LOH in their metastatic melanoma was more apparent in AJCC stage III than stage IV melanoma (log-rank test; p=0.03, p=0.81, respectively) and the APAF-1 LOH in RLM had a significantly worse survival outcome (log-rank test, p=0.02) compared to APAF-1 LOH in ITM (log-rank test, p=0.17) (page 26, lines 12-15 and lines 25-28 and page 27, lines 1-3 of the specification.)

In view of the forgoing, Applicants submit that claims 1, 6, 17, 26, 35, 44, 58, and 93, as well as the claims dependent from them, are fully enabled by the specification. Withdrawal of the rejection is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH – WRITTEN DESCRIPTION

Claims 1-3, 5-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 also stand rejected for lack of written description because these claims involve "any" marker at 12q22-23, "any" cancer, or "any" subject. Applicants submit that the rejection has been overcome by the amendments to these claims as discussed in detail above. Withdrawal of the rejection is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 74-80 stand rejected for being indefinite. More specifically, the Examiner stated that it is unclear if the combination is one, two, three, or four markers.

Applicants respectfully disagree. Claim 74 reads as follows:

> 74. The method of claim 1, wherein the DNA markers include a combination of D12S1657, D12S393, D12S1706, and D12S346. (Emphasis added.)

There is nothing ambiguous about the number of markers in the combination, i.e., the combination is a four-marker combination. Therefore, the metes and bounds of claim 74 are clear. Claims 75-80 have been canceled without prejudice, rendering the rejection moot in respect of these claims. Applicants respectfully request withdrawal of the rejection.

CLAIM REJECTIONS UNDER 35 USC § 102

Claims 1, 5-6, 10-13, 17, 21-22, 26, 30-31, 35, 39-40, 58-59, 63-64, 74-78, and 80 stand rejected as being anticipated by Soengas et al. (2001) Nature 409:207-211 ("Soengas"). Applicants respectfully traverse.

Claims 1 and 6, as amended, involve analyzing markers on DNA that exists as acellular DNA in human. This is not taught by Soengas, because Soengas analyzes cellular DNA from melanoma samples (page 207, right column, lines 14-15). Since Soengas fails to teach every limitation of claims 1 and 6, it cannot anticipate claims 1 and 6, or their dependent claims.

New claim 93 involves detecting colon or breast cancer by analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346. Since Soengas teaches nothing about colon or breast cancer, it cannot anticipate claim 93 or its dependent claims.

Claims 17 and 26, as amended, involve association of LOH of D12S1657, D12S393, D12S1706, and D12S346 with a high probability of a metastatic or progressing melanoma or colon cancer. Soengas does not teach either of the methods. First, Soengas teaches nothing about colon cancer. Secondly, Soengas finds a high rate of LOH of the microsatellite markers in metastatic melanoma samples (page 207, right column, lines 17-20). However, it provides no information about LOH of the microsatellite markers in primary melanoma samples, nor does it suggest that the high rate is statistically relevant to metastasis. Without such knowledge, Soengas fails to teach the association of LOH of the microsatellite markers with a high probability of a metastatic or progressing cancer.

Furthermore, Soengas determines LOH of APAF-1 based on the analysis of the microsatellite markers. It compares the expression of APAF-1 in metastatic melanoma samples where LOH of APAF-1 has been identified and primary melanoma samples. In view of this comparison, Soengas suggests that loss of APAF-1 may be associated with disease progression. See page 207, right column, line 20 – page 208, left column, line 4 of Soengas. However, such finding cannot be translated to the methods of claims 17 and 26 for three reasons. First, Soengas provides no information about LOH of APAF-1 in primary melanoma samples. Secondly, although Soengas finds that the expression of APAF-1 in metastatic melanoma samples where LOH of APAF-1 has been identified is less than that in

primary melanoma samples, it does not demonstrate any statistical relevance of this result. Finally, in Soengas, the APAF-1 gene was mapped to a position between D12S1657 and D12S393. As pointed out at page 28, line 27 – page 29, line 6 of the present specification, the correct location of the APAF-1 gene is between D12S1706 and D12S346. Because Soengas mapped the APAF-1 gene to a location more than 0.3 Mb away from the correct location, the relationship between the microsatellite markers and the APAF-1 gene was significantly wrong in Soengas. Consequently, if one skilled in the art relies on the value of the LOH of APAF-1 as determined in Soengas to determine the probability of a metastatic or progressing cancer, the prediction would not be correct. Therefore, Soengas fails to teach the association of LOH of APAF-1 with metastatic or progressing melanoma, much less the association of LOH of the microsatellite markers with metastatic or progressing melanoma.

In sum, since Soengas fails to teach association of LOH of D12S1657, D12S393, D12S1706, and D12S346 with a high probability of a metastatic or progressing melanoma or colon cancer, it cannot anticipate claims 17 and 26, or their dependent claims.

Claims 35 and 58, as amended, involve association of LOH of D12S1657, D12S393, D12S1706, and D12S346 with poor efficacy of a melanoma biochemotherapy in a human subject or a low probability of responsiveness to the biochemotherapy by a human subject. Soengas does not teach either of the methods. More specifically, Soengas finds that APAF-1 negative melanoma cell lines are resistant to ADR, a chemotherapeutic agent (page 209, left column, lines 8-10). However, it is well known in the art that in vitro experiments do not necessarily reflect the conditions in vivo. Therefore, the result in Soengas cannot be interpolated to be applicable in human subjects. As such, Soengas cannot anticipate claims 35 and 58, or their dependent claims, because it fails to teach association of LOH of the markers with poor efficacy of a melanoma

biochemotherapy in a human subject or a low probability of responsiveness to the biochemotherapy by a human subject.

In view of the foregoing, Applicants respectfully submit that claims 1, 6, 17, 26, 35, 44, 58, and 93, as well as the claims dependent from them, are novel over Soengas. The rejection should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 103

Claims 1-3, 5-8, 10-13, 17-19, 21-22, 26-28, 30-31, 35-37, 39-40, 58-61, 63-64, 74-78, and 80 stand rejected as being unpatentable over Soengas in view of U.S. Patent No. 6,156,504 to Gocke et al. ("Gocke"). Applicants respectfully traverse.

Soengas, as discussed in detail above, does not teach the following: (1) detecting colon or breast cancer by analyzing DNA markers including D12S1657, D12S393, D12S1706, and D12S346 in respect of claim 93; (2) association of LOH of the markers with a high probability of a metastatic or progressing melanoma or colon cancer in respect of claims 17 and 26; (3) association of LOH of the markers with poor efficacy of a melanoma biochemotherapy in a human subject or a low probability of responsiveness to the biochemotherapy by a human subject in respect of claims 35 and 58. Gocke discloses detection of extracellular tumor-associated nucleic acid in blood plasma or serum. It does not disclose detection of D12S1657, D12S393, D12S1706, or D12S346, much less the association of LOH of the markers with the presence of colon or breast cancer, a high probability of a metastatic or progressing melanoma or colon cancer, poor efficacy of a melanoma biochemotherapy in a human subject, or a low probability of responsiveness to the biochemotherapy by a human subject. Therefore, Gocke cannot cure the deficiencies of Soengas in respect of claims 93, 17, 26, 35, and 58. Indeed, the Examiner did not rely on Gocke for doing so.

With regard to claims 1 and 6, Soengas fails to teach analyzing DNA markers in the 12q22-23 region extending from D12S1657 to D12S346 (e.g., D12S1657, D12S393, D12S1706, and D12S346) on DNA that exists as acellular DNA in human.

To the contrary, Soengas analyzes D12S1657, D12S393, D12S1706, and D12S346 on cellular DNA from melanoma samples. Gocke, on the other hand, discloses detection of extracellular tumor-associated nucleic acid in blood plasma or serum. It is the Examiner's position that one skilled in the art would have been motivated to use the plasma or serum samples taught by Gocke in the method of Soengas with a reasonable expectation of success. Applicants respectfully disagree.

It is well known in the art that acellular DNA is quickly degraded in a human body. As a result, detection of markers in one region on a chromosome does not allow one skilled in the art to reasonably expect detection of other markers in another region on the same chromosome, much less another chromosome. Gocke does not indicate at all that DNA markers in the 12q22-23 region extending from D12S1657 to D12S346 (e.g., D12S1657, D12S393, D12S1706, and D12S346) are detectable. Because of the unpredictable nature of acellular DNA in a human body, one skilled in the art would not have been motivated to use the plasma or serum samples taught by Gocke in the method of Soengas; even if one skilled in the art would have been motivated to do so, there would have been no reasonable expectation of success.

In conclusion, claims 1 and 6 are non-obvious over the cited art for lack of motivation and reasonable expectation of success. Claims 17, 26, 35, 58, and 93 are non-obvious over the cited art because Soengas and Gocke, alone or in combination, do not add up to the claimed invention. The claims dependent from claims 1, 6, 17, 26, 35, 58, and 93 are patentable for at least the same reasons. Withdrawal of the rejection is thus respectfully requested.

DOUBLE PATENTING

Claims 1, 6, 17, and 26 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of co-pending U.S. Patent Application No. 10/809,956. If the pending claims in either application are found to be otherwise allowable except for

this ground of rejection, Applicants will submit an appropriate terminal disclaimer. In this event, Applicants request that the Examiner telephone the undersigned who will then provide the terminal disclaimer.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned agent at the Los Angeles, California telephone number (310)785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: February 28, 2007

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